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Polypharmacy and inappropriate medication use in patients with dementia: an underresearched problem

Abstract

Multimorbidity and polypharmacy are increasingly prevalent across healthcare systems and settings as global demographic trends shift towards increased proportions of older people in populations. Numerous studies have demonstrated an association between polypharmacy and potentially inappropriate prescribing (PIP), and have reported high prevalence of PIP across settings of care in Europe and North America and, as a consequence, increased risk of adverse drug reactions, healthcare utilisation, morbidity and mortality. These studies have not focused specifically on people with dementia, despite the high risk of adverse drug reactions and PIP in this patient cohort. This narrative review considers the evidence currently available in the area, including studies examining prevalence of PIP in older people with dementia, how appropriateness of prescribing is assessed, the medications most commonly implicated, the clinical consequences, and research priorities to optimise prescribing for this vulnerable patient group. Although there has been considerable research effort to develop criteria to assess medication appropriateness in older people in recent years, the majority of tools do not focus on people with dementia. Of the limited number of tools available, most focus on the advanced stages of dementia in which life-expectancy is limited. The development of tools to assess medication appropriateness in people with mild-to-moderate dementia or across the full spectrum of disease severity represents an important gap in the research literature and is beginning to attract research interest, with recent studies considering the medication regimen as a whole, or misprescribing, overprescribing or underprescribing of certain medications/medication classes including anticholinergics, psychotropics, antibiotics and analgesics. Further work is required in development and validation of criteria to assess prescribing appropriateness in this vulnerable patient population, to determine prevalence of PIP in large cohorts of people with the full spectrum of dementia variants and severities and to examine the impact of PIP on health outcomes.

Keywords

Adverse drug reaction, comorbidity, dementia, inappropriate medication use, inappropriate prescribing, polypharmacy.

Introduction

The world's population is ageing at an increasingly dramatic rate as fertility rates fall and people in high-, middle- and low-income countries are living longer [World Health Organization, 2015].

Multimorbidity, commonly defined as the presence of two or more chronic medical conditions [World Health Organization, 2015] and, as a consequence, polypharmacy (the prescribing of multiple medications) are increasingly prevalent across healthcare systems and settings in most developed countries [Cadogan *et al.* 2016] as demographic trends shift towards increased proportions of older persons in their populations. Coupled with age-related changes in drug pharmacokinetics and pharmacodynamics, multimorbidity and polypharmacy are widely regarded as key predisposing factors for adverse drug reactions (ADRs) [Mangoni & Jackson, 2004; Viktil *et al.* 2007; Cherubini *et al.* 2011; Petrovic *et al.* 2012; Onder *et al.* 2013].

It is widely recognised that there is no universally accepted definition of “polypharmacy” [Cadogan *et al.* 2016]; it has been defined as the prescribing of medications over a threshold number of four or five [Maher *et al.* 2014; Patterson *et al.* 2014], or may be considered conceptually to describe the prescribing of “many drugs” or “too many” drugs [Cadogan *et al.* 2016], introducing a dimension in which the appropriateness of the prescribing is taken into account [Aronson, 2004]. Irrespective of the lack of a universally recognised definition of the term, numerous studies have highlighted the association between polypharmacy and inappropriate medication use in older people [Cadogan *et al.* 2016; Bradley *et al.* 2012; Cahir *et al.* 2010]. Medicines are considered to be prescribed appropriately when they have a clear evidence-based indication, are cost-effective and well-tolerated [O’Mahony & Gallagher, 2008]. Inappropriate medication use, inappropriate drug use (IDU), inappropriate prescribing (IP) and potentially inappropriate prescribing (PIP) are terms used to refer to suboptimal prescribing practices which include overprescribing, underprescribing and misprescribing of medications [Spinewine *et al.* 2007; Kaufmann *et al.* 2014]. The (in)appropriateness of prescribing for older people has received significant research attention in recent years, with numerous studies reporting high prevalence of PIP in acute and long-term care settings and in community-dwelling older people in Europe and North America and demonstrating its association with increased risk of ADRs, morbidity, mortality and healthcare utilisation [Fialova *et al.* 2005; Fu *et al.* 2007; Spinewine *et al.* 2007; Gallagher *et al.* 2008; Gallagher *et al.* 2011; Hamilton *et al.* 2011; García-Gollarte *et al.* 2012; Opondo *et al.* 2012; Hill-Taylor *et al.* 2013; Blanco-Reina *et al.* 2014; Galvin *et al.* 2014; Gosch *et al.* 2014; Kovačević *et al.* 2014; Shade *et al.* 2014; Tommelein *et al.* 2015]. However, few studies have focussed specifically on people with dementia [Montastruc *et al.* 2013].

Dementia is an irreversible neurodegenerative disorder characterised by a cluster of signs and symptoms including difficulties in memory, disturbances in language, psychosocial and psychiatric changes, and impairments in activities of daily living [Burns & Iliffe, 2009; Wu *et al.* 2016]. It is commonly associated with other chronic medical conditions such as diabetes, chronic obstructive

pulmonary disease, chronic cardiac failure, musculoskeletal disorders, and vascular disease [Bell *et al.* 2015; Doraiswamy *et al.* 2002; Schubert *et al.* 2006; Lee *et al.* 2009; Onder *et al.* 2012], and as a consequence, polypharmacy [Onder *et al.* 2013]. It has been reported that people with dementia take an average of 5-10 medications, of which 1-2 are prescribed for dementia and the remainder are indicated for the treatment of other comorbid medical conditions [Elmståhl *et al.* 1998; Lau *et al.* 2010]. The use of multiple medications in this population raises a number of issues; memory loss, decline in intellectual function, and impaired judgement and language may cause difficulties in communicating symptoms or problems related to adverse effects of drugs [Ganjavi *et al.* 2007; Onder *et al.* 2011]. Furthermore, older people, and those with dementia in particular, are often excluded from clinical trials and guidelines, so the evidence base to guide prescribing for these patients is limited [Brauner *et al.* 2000; Marengoni & Onder, 2015]. Finally, people with dementia have a reduced life expectancy, which may impact on the risk-benefit profile of a medication; drugs for primary or secondary prevention may require years of treatment to demonstrate their benefit, and their use may be considered inappropriate if a patient is not expected to survive to realise this benefit [Currow & Abernethy, 2006; Fusco *et al.* 2009; Holmes, 2009; Onder *et al.* 2013].

In this narrative review article we discuss the prevalence of PIP in older people with dementia, giving consideration to how appropriateness is assessed, the medications which are most commonly implicated in PIP, the clinical consequences of such prescribing, and research priorities to optimise prescribing for this vulnerable patient group.

Search methodology

A literature search was conducted using MEDLINE (1950–January 2016), EMBASE (1980– January 2016), Web of Science (1981– January 2016), International Pharmaceutical Abstracts (1970– January 2016) and the Cochrane Library of Systematic Reviews (1999–January 2016). The search terms used were “inappropriate”, “potentially inappropriate”, “dementia”, “Alzheimer”, “drugs”, “medicines”, “medications”, “prescribing”, “prescription”, “older”, “old”, “elderly”, “aged” and combinations thereof. Only articles in the English language were selected. No attempt was made to reject papers on the basis of methodology, e.g. not a randomized controlled trial, as some studies were descriptive in nature or were papers that were classified as commentaries.

Medication appropriateness in people with dementia

There has been considerable effort to develop criteria to classify the appropriateness of medication use in older people in recent years, resulting in the evolution and refinement of a number of tools. These utilise implicit (judgement-based) or explicit (criterion-based) measures of medication

appropriateness, or a combination of both approaches [Kaufmann *et al.* 2014]. A recent systematic review found 46 available tools, each with limitations, strengths and weaknesses [Kaufmann *et al.* 2014]. These tools varied in their target populations; while most named older people as target patients, just over 20% did not specify an age group. The majority (59%) did not specify healthcare setting, some focused on hospitalised patients, while others considered ambulatory care or long-term care [Kaufman *et al.* 2014]. The Beers criteria [Beers *et al.* 1991; Beers, 1997; Fick *et al.* 2003; Campanelli, 2012; American Geriatrics Society, 2015] and the Screening Tool of Older Person's Prescriptions (STOPP) – Screening Tool to Alert doctors to Right Treatment (START) criteria [Gallagher *et al.* 2008; O'Mahony *et al.* 2014] are probably the best known and most widely studied of these tools in US and European settings respectively. These tools, and others developed since the publication of the systematic review by Kaufmann *et al.* [Renom-Guiteras *et al.* 2015], do not specifically consider older people with dementia [Kröger *et al.* 2015; Montastruc *et al.* 2013]; there is a paucity of studies relating to the development and application of criteria specifically for assessing appropriateness of medication for this patient population.

PIP in people with dementia has been understudied to date [Montastruc *et al.* 2013; Johnell 2015; Sköldunger *et al.* 2015], but is gaining research interest, as indicated by the recent publication of a number of studies focusing on this particularly vulnerable cohort. Much of this work, discussed below, has focussed on people with advanced dementia (characterised by profound cognitive deficits, inability to recognize family members, speech limited to fewer than 5 words, total functional dependence, incontinence, and inability to ambulate [Mitchell *et al.* 2012]) and limited life expectancy. These studies are summarised in Table 1.

INSERT TABLE 1 HERE

The most significant advance in the literature in this area was the development of consensus criteria for appropriate prescribing by Holmes *et al.* [Holmes *et al.* 2008]. These criteria have since been applied in a number of other studies in the USA and Europe (Table 1). More recently, Kröger *et al.* undertook a scoping review of criteria on medication appropriateness in severe dementia and characteristics of intervention studies [Kröger *et al.* 2015]. This revealed that although considerable attention had been devoted to inappropriateness of medication use among older residents of nursing homes, comprehensive specific criteria were limited to the Holmes *et al.* list. Following the publication of this review, Parsons *et al.* presented medication appropriateness indicators for persons with advanced dementia specific to the UK context developed using a similar approach to Holmes *et al.* [Parsons *et al.* 2015], details of which are outlined in Table 1. To the best of the author's knowledge, the criteria identified by Holmes *et al.* (2008) and Parsons *et al.* (2015)

represent the only currently available systems for identifying PIP in people with advanced dementia in whom a palliative approach is needed.

Studies including people with mild-to-moderate dementia or recruiting across the full spectrum of disease severity are now beginning to appear in the research literature. Summarised in Table 1, these studies focus on the medication regimen as a whole, or on several medications or medication classes. They demonstrate the high prevalence of PIP across disease severity and setting and country of care, and the necessity for development and validation of tools to assess appropriateness of prescribing specifically for people with dementia. Expanding the evidence base in this area is of critical importance due to the adverse health, clinical and economic outcomes associated with inappropriate drug use among older people with dementia [Sköldunger *et al.* 2015].

In addition to this body of work, some studies have considered misprescribing, overprescribing, or underprescribing of individual medications or medication classes, as outlined below. Considerable scope exists to improve the quality of prescribing for people with dementia in each of these areas.

Appropriateness of prescribing of specific drug classes

Anticholinergic medications

Older people are commonly subjected to a high anticholinergic load or burden due to the widespread use of anticholinergic/antimuscarinic medications and the wide range of medications possessing anticholinergic side-effects (such as antihistamines, antidepressants, anti-Parkinson agents, antipsychotics, antispasmodics, and skeletal muscle relaxants) [Mate *et al.* 2015]. People with dementia are particularly susceptible to adverse effects associated with a high anticholinergic load [Sunderland *et al.* 1987; Sunderland *et al.*, 1985; Sura *et al.* 2013]; they have reduced levels of acetylcholine (a neurotransmitter critical to the neurons involved in cognition), and as a consequence anticholinergic medications may worsen their cognitive function [Feinberg 1993; Roe *et al.* 2002; Carnahan *et al.* 2004; Kemper *et al.* 2007; Rudolph *et al.* 2008; Carrière *et al.* 2009; Modi *et al.* 2009; Fox *et al.* 2011].

Studies have demonstrated a high anticholinergic load among people with dementia; work conducted in the United States, Australia and the UK have reported that between 40 and 60% of patients with dementia use at least one anticholinergic medication [Chan *et al.* 2006; Bhattacharya *et al.* 2011; Sura *et al.* 2013; Mate *et al.* 2015; Cross *et al.* 2016], with 10 – 25% using higher potency anticholinergic drugs or medications with clinically significant anticholinergic activities [Bhattacharya *et al.* 2011; Sura *et al.* 2013; Mate *et al.* 2015; Palmer *et al.* 2015; Cross *et al.* 2016]. Due to the association of anticholinergic burden with falls, worsening cognition and worsening function [Moore

& O'Keefe, 1999; Tune, 2001; Cao *et al.* 2008; Lowry *et al.* 2011; Uusvaara *et al.* 2011], clinicians should consider the anticholinergic properties of medications when adding to or changing patients' drug regimens, with a view to minimising the anticholinergic effects [Palmer *et al.* 2015].

Psychotropics

Psychotropic drugs, including antipsychotics, anxiolytics, hypnotics, antidepressants, anticonvulsants and antidementia drugs, are widely prescribed for behavioural and psychological symptoms of dementia (BPSD) [Thompson Coon *et al.* 2014; van der Spek *et al.* 2015], which include behaviours such as aggression, screaming, restlessness, anxiety, hallucinations and depressive mood [Cerejeira *et al.* 2012]. These neuropsychiatric symptoms are highly prevalent in people with dementia; up to 90% of people with Alzheimer's disease experience at least one symptom during the course of the disease [Liperoti *et al.* 2008].

Treatment guidelines for BPSD recommend that antipsychotics should not be used as first-line management; detailed assessment to rule out other treatable causes of symptoms and alternative nonpharmacological interventions should be tried first [Food and Drug Administration, 2005; National Institute for Health and Care Excellence, 2006; Food and Drug Administration, 2008; European Medicines Agency, 2010; Chiu *et al.* 2015; Foebel *et al.* 2016]. Antipsychotics are unlicensed for treatment of these symptoms [Muench & Hamer, 2010], with the exception of risperidone, which has approval for this indication in some countries [Langballe *et al.* 2014]. Furthermore, they have demonstrated limited efficacy and have been associated with serious side-effects, increased morbidity, exacerbation of functional and cognitive decline, and mortality [Schneider *et al.* 2005; Kales *et al.* 2007; Liperoti *et al.* 2009; Trifirò *et al.* 2009; Ballard *et al.* 2011; Musicco *et al.* 2011; Huybrechts *et al.* 2012; Langballe *et al.* 2014; Bonner *et al.* 2015; Foebel *et al.* 2016]. Despite this, they continue to be prescribed frequently, often on an unlicensed, long-term basis. As a result, the appropriateness of antipsychotic use in this population is often questioned [Chiu *et al.* 2015; Foebel *et al.* 2016], and it has been estimated that two-thirds of prescriptions are unnecessary [Ballard *et al.* 2014]. Although rates of antipsychotic prescribing in older people with dementia are declining in response to warnings from agencies such as the US Food and Drug Administration (Food and Drug Administration 2005; Food and Drug Administration 2008), the European Medicines Agency [European Medicines Agency, 2010] and the UK Department of Health [Banerjee, 2009], antipsychotic use remains widespread, particularly in long-term care settings. Recent rates of antipsychotic prescribing have been reported to range from 7.4% in primary care and 16.6% in acute care in the UK [Martinez *et al.* 2013; Stephens *et al.* 2014], to 25% across care settings in Germany [Schulze *et al.* 2013], 31% in institutional care settings in the Netherlands

[Kleijer *et al.* 2014], and 40% in geriatric care settings in Sweden [Lövhelm *et al.* 2006]. In the United States, the 2004 National Nursing Home survey (NNHS) reported that approximately one-third (32.9%) of nursing home residents with dementia received at least one antipsychotic medication [Kamble *et al.* 2009]. More recent figures suggest that patterns of prescribing in the US have not changed considerably; 23.9% of all long-stay nursing home residents received at least one antipsychotic medication [Centres for Medicare and Medicaid Services, 2011]. Future research should aim to continue to gather and apply research evidence to improve the safety and quality of antipsychotic prescribing, and to address a number of key unanswered questions regarding the mortality risk of drugs at the individual drug level, the relationship between dose and mortality, and the individual patient factors which may predispose or mitigate risk [Ballard *et al.* 2014].

Antibiotics

People with dementia are susceptible to infections, including respiratory tract infections (RTIs), urinary tract infections (UTIs), and skin and soft tissue infections [Mitchell *et al.* 2009; Vandervoort *et al.* 2013]. Treatment decisions, particularly in the more advanced stages of dementia and at the end of life, are complex [van Der Maaden *et al.* 2015] and require a balance of the potential burden caused by treatment, the best interests of the patient, and family and patient preferences [van der Steen *et al.* 2001; Hurley & Volicer, 2002]. This complexity is due in part to the inability of patients to communicate their symptoms, and because typical symptoms of infections are often absent [Scherder *et al.* 2009; D'Agata *et al.* 2013].

Much work has been undertaken to examine potentially inappropriate antimicrobial use in older people residing in long-term care settings [Zimmer *et al.* 1986; Warren *et al.* 1991; Pickering *et al.* 1994; Montgomery *et al.* 1995; Loeb *et al.* 2001; Lim *et al.* 2012; Phillips *et al.* 2012; Stuart *et al.* 2012; Peron *et al.* 2013; Sloane *et al.* 2014; van Buul *et al.* 2015], reporting asymptomatic bacteriuria as the most common reason for potentially inappropriate antibiotic use [Pickering *et al.* 1994; Loeb *et al.* 2001; Nicolle, 2002; Black *et al.* 2006; Phillips *et al.* 2012; D'Agata *et al.* 2013; van Buul *et al.* 2015]. However, there has been limited work undertaken to date to examine the appropriateness of antibiotic prescribing specifically in people with dementia [Mitchell *et al.* 2014]. One study of US nursing home residents with advanced dementia reported that 44% of treated episodes of suspected infection met minimum clinical criteria [Loeb *et al.* 2001] for initiation of antimicrobial treatment, suggesting that much of the extensive prescription of antimicrobials in advanced dementia may be unwarranted [Mitchell *et al.* 2014]. The authors reported that antibiotics were most likely to be initiated in the absence of minimum treatment criteria for UTIs which rely on subjective signs and symptoms undetectable to the observer in the absence of patient self-report.

They highlighted the difficulty in interpreting what is “symptomatic” in people with advanced dementia and in applying minimum criteria for treatment. The development of consensus criteria to measure appropriateness of prescribing, specific to people with dementia and comprising indicators of appropriate prescribing of antimicrobials, would facilitate a more judicious approach to infection management in this vulnerable patient population, avoiding unnecessary treatment burden and mitigating the threat of multidrug resistant organisms [Mitchell *et al.* 2014].

Analgesics

It has been widely reported that approximately 50% of older people with dementia experience pain [Leong & Nuo, 2007; Zwakhelen *et al.* 2009; Barry *et al.* 2016], which is often chronic in nature and caused by musculoskeletal conditions, previous fractures or neuropathies [Hadjistavropoulos *et al.* 2007; Scherder & Plooi, 2012]. Despite this, there is evidence that pain in dementia often remains undetected and undertreated [Hoffmann *et al.* 2014; Tan *et al.* 2015]. A number of possible reasons for this have been suggested; people with dementia have difficulty in expressing and communicating their pain [Marzinski 1991; Ferrell *et al.* 1995; Cook *et al.* 1999; Husebo *et al.* 2008; Reynolds *et al.* 2008], it can be difficult for observers to identify pain which can manifest in a range of behaviours and symptoms also indicative of other forms of distress including depression, boredom or anxiety [Breland *et al.* 2015], and physicians may be reluctant to prescribe medications, particularly opioids, for these patients due to higher rates of treatment complications [Closs *et al.* 2004; Pickering *et al.* 2006; Corbett *et al.* 2012; Monroe *et al.* 2014; Breland *et al.* 2015; Li *et al.* 2015]. Furthermore, a lack of pharmacological studies examining the pharmacodynamic properties of analgesics in this vulnerable patient population [McLachlan *et al.* 2011] may result in treatment decisions made in the absence of a clear knowledge of the impact of comorbidities on the efficacy and adverse effect profiles of analgesics [Achterberg *et al.* 2013].

It has been hypothesised that people with dementia may perceive and express pain differently to cognitively intact individuals; however, to date, many studies examining pain and analgesic use in people with dementia have utilised pain assessment scales or instruments which are not specific to this patient population [Scherder *et al.* 2003; Corbett *et al.* 2012; Tan *et al.* 2015]. Future research is required using dementia-specific pain scales [Achterberg *et al.* 2013; Tan *et al.* 2015] and considering the neuropathology, experience, assessment and management of pain in these vulnerable patients [Tan *et al.* 2015]. The appropriateness of pharmacological treatments for people with dementia, considering the use of different analgesic classes and doses, as part of a standardised approach to pain management, is a research priority [Tan *et al.* 2015].

Priorities for research

Further studies of PIP in large cohorts of people with dementia and cognitive impairment, which include patients across the spectrum of variants and dementia severities, are required [Johnell, 2015; Sköldunger *et al.* 2015]. In order to undertake these studies, it is imperative that prescribing appropriateness criteria specific to this patient population are developed and/or utilised, which take into consideration the most commonly implicated medications discussed in this narrative review; namely anticholinergics, psychotropics, antibiotics and analgesics, in addition to drug-drug and drug-disease interactions. Such criteria must consider dementia of all severities and be applicable across settings of care. Future work should also examine the impact of PIP on health outcomes for persons with dementia [Hanlon *et al.* 2015], an area which has received little research attention to date.

Conclusion

Older adults with dementia are at risk of suboptimal and potentially inappropriate prescribing. Evidence-based guidelines to assist physicians in prescribing for these vulnerable patients, who often have multiple co-morbidities and take multiple medications, are lacking. The pharmacotherapeutic management of these patients is an area requiring urgent research attention.

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Conflict of interest statement

The author declares no conflict of interest in preparing this article.

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Table 1. Summary of studies determining medication appropriateness in people with dementia

Author/Year (Country)	Sample, N	Design	Definition of Medication Appropriateness	Study findings
Holmes <i>et al.</i> 2008 (USA)	34 residents with advanced dementia (FAST score 6E, 7A, 7B or 7C [Reisberg, 1988]) in 3 long-term care facilities	Feasibility study developing consensus recommendation for appropriate prescribing in people with advanced dementia in whom palliation of symptoms is the primary goal of therapy, using modified Delphi consensus process (12 geriatricians), and medication record review	Medications categorised into: never, rarely, sometimes or always appropriate for use in patients with advanced dementia	Consensus was reached on appropriateness of 69 of 81 medications and medication classes. 5% of 221 medications prescribed at enrolment were considered to be never appropriate, and 10 of 34 patients (29%) were taking a never appropriate medication
Tjia <i>et al.</i> 2010, (USA)	323 residents with advanced dementia (GDS score of 7 [Reisberg <i>et al.</i> 1982]) in 22 nursing homes	Medication record review of data collected in the CASCADE study (Mitchell <i>et al.</i> 2006)	Prescribing of drugs deemed never appropriate in advanced dementia according to Holmes <i>et al.</i> (2008)	37.5% received at least one medication considered never appropriate in advanced dementia. Most commonly implicated inappropriate medications were AChEIs (15.8%), lipid-lowering agents (12.1%) and

Colloca <i>et al.</i> 2012 (Europe [Czech Republic, Finland, France, Germany, Italy, The Netherlands, UK] and Israel)	1449 residents with severe cognitive impairment (CPS score of 4 – 6 [Morris <i>et al.</i> 1994]) in 57 nursing homes	Medication record review of data collected in the SHELTER study (Onder <i>et al.</i> 2012)	Prevalence of prescribing drugs classified by Holmes <i>et al.</i> (2008) as rarely or never appropriate in advanced dementia	memantine (9.9%) Inappropriate drug use observed in 643 (44.9%) of residents. Most commonly implicated medications were lipid-lowering drugs (9.9%), antiplatelet agents excluding acetylsalicylic acid (9.9%), AChEIs (7.2%) and antispasmodics (6.9%).
Parsons <i>et al.</i> 2012 (UK)	Residents with dementia (documented diagnosis or cognitive impairment indicative of dementia determined by senior care home staff) in 6 residential care homes (n=119, timepoint 1; n=110, timepoint 2)	Retrospective analysis of medication data	Prescribing of potentially PIMs, using 31 from 65 STOPP criteria.	55 residents (46.2%) and 45 residents (40.9%) prescribed \geq 1 PIM at timepoints 1 and 2 respectively. Long-term antipsychotics more frequently prescribed PIM; for 21.0% and 19.1% of residents at timepoints 1 and 2.
Montastruc <i>et al.</i> 2013 (France)	684 community-dwelling people with mild-to-moderate AD (MMSE 10-26 [Folstein <i>et al.</i> 1975])	Analysis of medication data collected in prospective multicentre cohort study	Prescribing of PIMs according to the 2003 Beers criteria (Fick <i>et al.</i> 2003), the Laroche list (Laroche <i>et al.</i> 2007) and a further list of atropinic drugs	Approximately one-quarter (25.3%) of patients were prescribed \geq 1 PIM according to the Beers criteria, and 46.8% were

			defined by the research team.	prescribed at least one PIM according to the Laroche list 46.8% of patients were prescribed ≥ 1 PIM. Cerebral vasodilators were the most widely used class (24% of all prescriptions), followed by atropinic drugs (17%) and long half-life benzodiazepines (8.5%). Atropinic drugs were associated AChEIs in 16% of patients.
Toscani <i>et al.</i> 2013 (Italy)	245 residents in 34 nursing homes and 165 community dwelling people with advanced dementia (FAST score ≥ 7)	Medication record review of data collected in the EOLO-PSODEC study	Prescribing of drugs in appropriateness categories classified by Holmes <i>et al.</i> (2008)	21.2% of all participants prescribed never or rarely appropriate medications. Prescribing rates did not differ significantly between community-dwelling people with dementia and those resident in nursing homes.
Tjia <i>et al.</i> 2014 (USA)	5406 residents with advanced dementia	Medication record review of nationwide	Use of medications of questionable benefit	2911 (53.9) of residents received at

	(CPS score of 6) from Minimum Data Set facilities (460 facilities)	long-term care pharmacy database linked to the Minimum Data Set	(deemed never appropriate in advanced dementia by Holmes <i>et al.</i> 2008)	least one medication of questionable benefit. Most commonly implicated inappropriate medications were AChEIs (36.4%), memantine (25.2%) and lipid-lowering agents (22.4%)
Hanlon <i>et al.</i> 2015 (USA)	1303 veterans with dementia (identified using ICD-9 codes for AD, VaD and other dementias, including dementia not otherwise specified) resident in 133 Veterans Affairs Community Living Centers. Dementia severity defined using CPS and ADL (McConnell <i>et al.</i> 2002) scores.	Analysis of medication data collected during retrospective descriptive study	For patients with mild-moderate dementia, underuse was operationally defined as no pharmacy dispensing of an AChEI. In the severe dementia group, overuse was defined as use of medications/classes for which patients were unlikely to derive benefit given their limited life expectancy and the risk of adverse drug reactions (medications defined by Holmes <i>et al.</i> [2008] as “never appropriate” for use in these patients). PIM use was defined in both groups	Rates of PIP were 27.2% for people with mild-to-moderate dementia and 25.1% for those with severe dementia respectively. Potential underuse was observed in 70.2% of people with mild-to-moderate dementia, and potential overuse in 36.1% of those with severe dementia (23.4% receiving AChEIs and 12.8% a lipid-lowering agent). Approximately one-quarter (25.1%) of people with severe

			as evidence of clinically important drug-disease interactions (medications which may worsen cognitive function: anticholinergics, barbiturates, and benzodiazepine receptor agonists) or drug-drug interactions (highly anticholinergic drugs that can block the pharmacodynamics effects of AChEIs, or drugs which can inhibit the metabolism of galantamine or donepezil)	dementia had evidence of inappropriate prescribing as a result of a drug-drug or drug-disease interaction. In people with severe dementia, antipsychotic use was associated with all three types of suboptimal prescribing.
Parsons <i>et al.</i> 2015 (UK)	15 residents with advanced dementia (FAST score between 6E and 7F) from 3 nursing homes	Feasibility study developing consensus recommendation for appropriate prescribing in people advanced dementia in whom palliation of symptoms is the primary goal of therapy, using Delphi consensus process (9 clinicians including 4 geriatricians, 4 old age psychiatrists and 1	Medications categorised into: never, rarely, sometimes or always appropriate	14 residents at baseline were taking ≥ 1 never appropriate medication, and 25.7% of medications prescribed were never appropriate. Use of never appropriate medications did not change significantly at 3, 6 or 9 month

		neurologist), and longitudinal prospective medication record review		timepoints. For residents who died during data collection (n=4), there was a decrease in prescribing of never appropriate medications (12.0) and an increase in prescribing of always appropriate medications (28.0%)
Sköldunger <i>et al.</i> 2015 (Sweden)	4108 older people in the SNAC study (Lagergren <i>et al.</i> 2004), including 319 with dementia (diagnosed by a physician, according to DSM-III-R [American Psychiatric Association, 1987])	Analysis of medication data collected during prospective longitudinal cohort SNAC study	Prescribing of inappropriate drugs defined as exposure to at least one of the following: concurrent use of three or more psychotropic drugs, drugs with anticholinergic properties, long-acting benzodiazepines, and serious drug-drug interactions as defined by national guidelines.	Prevalence of inappropriate drug use was significantly higher in the cohort with dementia (27.3%) than for participants without dementia (n=3783), in whom prevalence was reported at 11.8%. For people with dementia, inappropriate drug use was associated with an increased risk of hospitalisation but the association between inappropriate drug use and mortality was not significant.

Cross <i>et al.</i> 2016 (Australia)	964 community-dwelling patients with mild cognitive impairment (Petersen criteria [Winblad <i>et al.</i> 2004] or dementia (DSM-IV), attending 9 memory clinics	Analysis of medication data from the PRIME multicentre observational study (Brodaty <i>et al.</i> 2011)	Prescribing of PIMs relating to cognitive impairment, utilising Beers 2012 criteria (Campanelli, 2012) and the STOPP 2014 criteria (O'Mahony <i>et al.</i> 2014).	21.4% of patients were using ≥ 1 PIMcog, and 4.8% were using ≥ 2 ; medications most commonly implicated were sedatives and anticholinergics.
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